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WO 01/21228 A1

(54) Title: CARDIAC VALVE AND METHOD FOR PREPARING A BIOLOGICAL TISSUE

(57) Abstract: The use of compounds with a ring of 6 carbon atoms having at least two hydroxyl groups as an agent against the calcification. Support, especially heart valves, treated with the said compounds.

Cardiac valve and method for preparing a biological tissue.

This invention relates to a cardiac valve made from a biological or biocompatible tissue having a resistance to calcification.

Cardiac valves are known from documents US5476516, US 5002566 and WO89/06945, which are made from biological tissues stabilized by an aldehyde, e.g. a glutaraldehyde, and which have been complementarily treated with a polyol, such as polypropylene glycol, butanediol, pentanediol, etc., or with a solution containing an iron or tin salt, or with an aliphatic carboxylic acid, or with an ester of such acid. Cardiac valves which have been treated as described in these documents have a more or less reduced calcification, but cannot suppress it totally.

In this invention, a family of particular compounds has been selected, providing an excellent calcification resistance. Further, in the case of a biological tissue, this selection of such compounds ensures that the tissue is stabilized and that its structure is preserved, both as regards proteins and lipids.

The cardiac valve according to the invention is made from a support associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

Advantageously, the valve is at least partially

made from a biological tissue and/or from a polymer or copolymer compound, particularly from a biopolymer compound, and/or from an at least partly cross-linked and biocompatible compound, said tissue and/or compound being associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

Advantageously, the valve according to the invention has, at least at its surface, a polymer or copolymer or an at least partly cross-linked compound, associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

According to a preferred embodiment, the valve consists of a tissue, particularly of a biological tissue, stabilized by a polymer or copolymer or an at least partly cross-linked compound, said compound, polymer or copolymer advantageously forming a network, said compound, polymer or copolymer being associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon. An appropriate biological tissue may be, for example, a biological tissue removed from the heart of an animal, or from the aortic valve of an animal, or from the pericardium of an animal, said tissue being advantageously stabilized by a cross-linkable compound, such as an aldehyde, particularly a glutaraldehyde, wherein the aldehyde (particularly the glutaraldehyde) which is at least at the surface of the tissue or in the proximity thereof is at least partially associated to a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

It has been noted that the use of such compounds

provided the cardiac valve with calcification resistance properties, with good mechanical properties, with easy rinse and/or sterilization features and, in the case of a biological tissue, with the possibility to preserve the structure thereof, both as regards proteins and lipids (phospholipids).

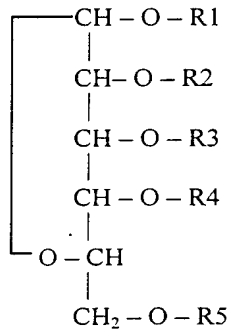
In accordance with possible embodiments, the valve is made from biopolymers, the composition of which can contain one or more substances selected from the group consisting of polylactic compounds, polyglycolic compounds, modified hyaluroic acid , collagen, fibrin, fibronectin, etc., and mixtures thereof.

Advantageously, the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, is selected from the group comprising tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of dehydroshikimic acid, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof.

By way of example, the following compounds may be mentioned:

* gallotannins, particularly

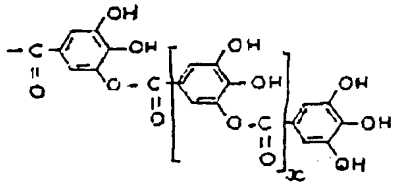
- tannins with formula



where R1 = R2 = R3 = R4 = the rest of gallic or digallic acid, and R5 = H; or

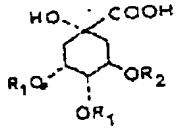
where R1, R2, R3, R4 and R5 are selected from the rest of gallic or digallic acid or

where R1 = R3 = R4 = the rest of gallic acid, R2 = H and R5 =



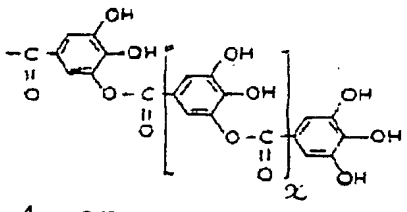
where x = 0, 1, 2, 3 or 4

- tannins with formula



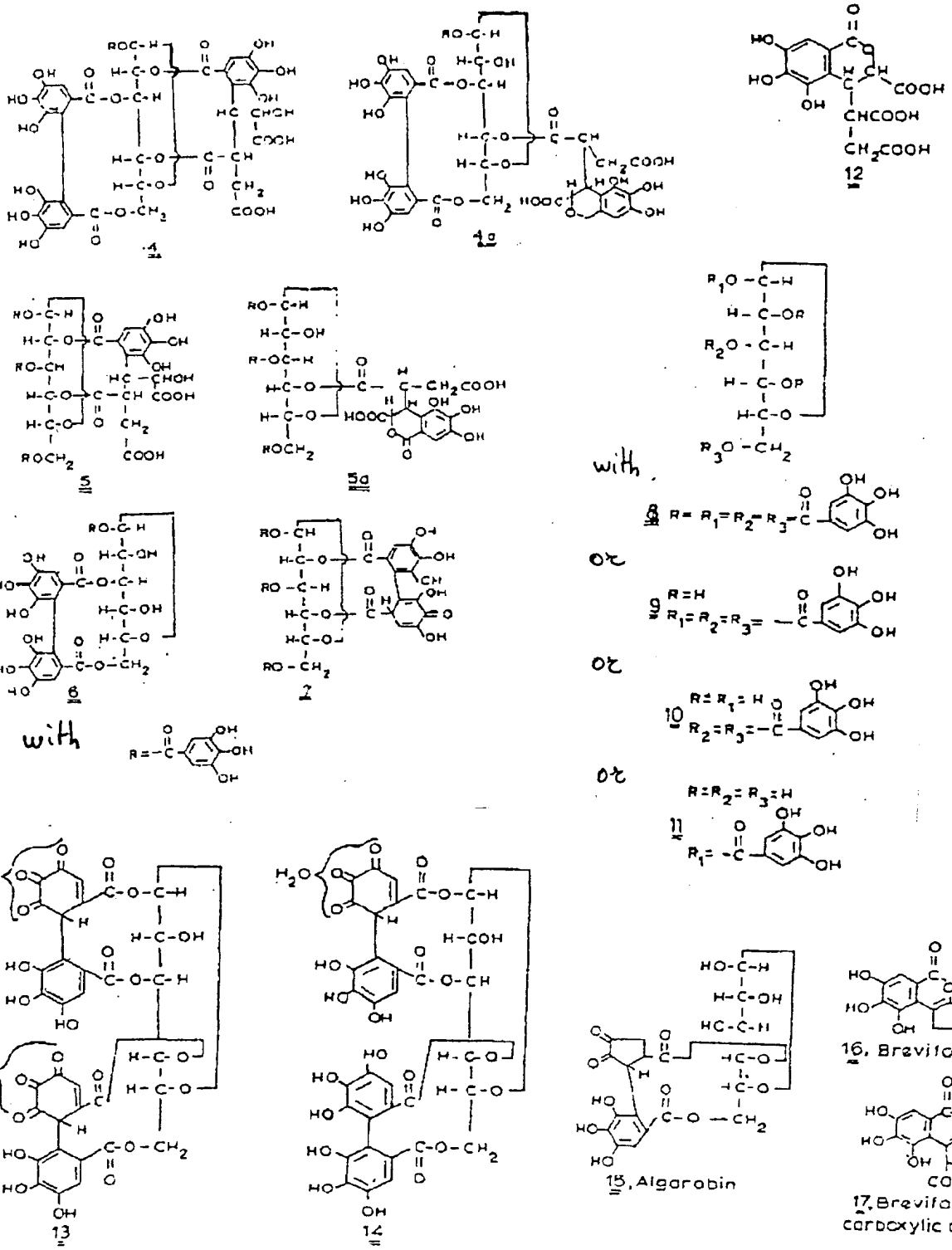
where R1 = the rest of gallic or digallic acid, and

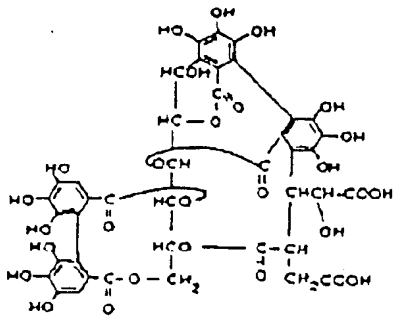
R2 =



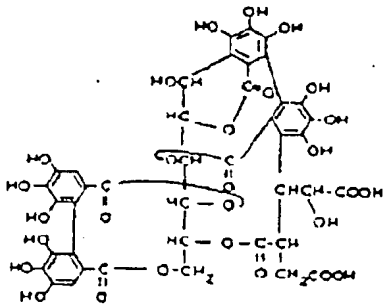
where x = 0, 1, 2, 3 or 4, or

* ellagitannins, particularly tannins with formula

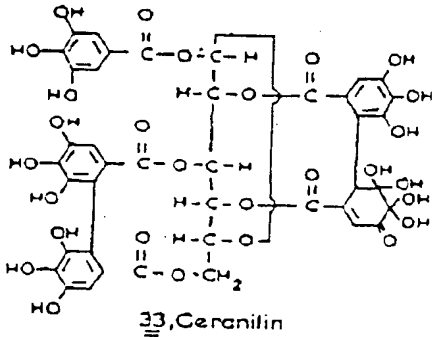




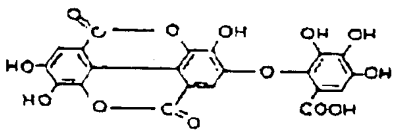
22, Valolaginic acid



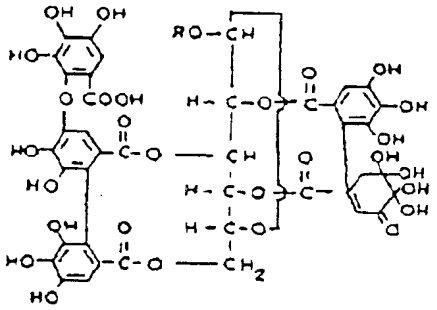
23, Isovalolaginic acid

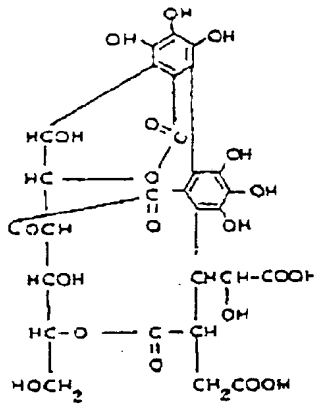


33, Geraniin

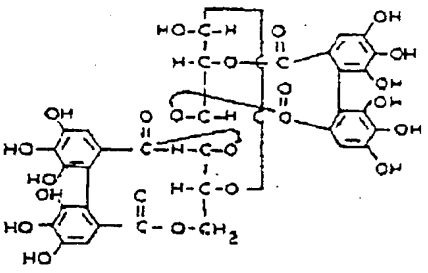


25, Valoneaic acid dilactone

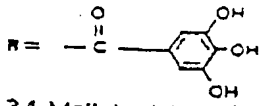




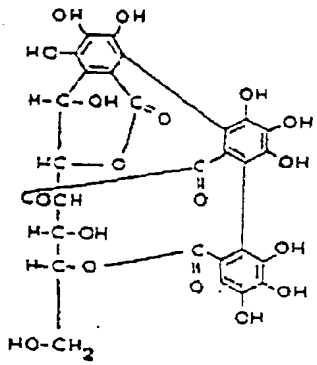
24, Valotinic acid



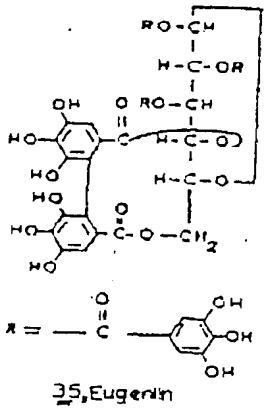
26, Pendunculagin



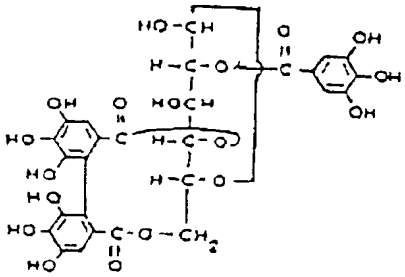
34, Mallotusinic acid



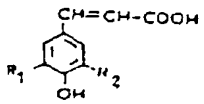
27, Castalin



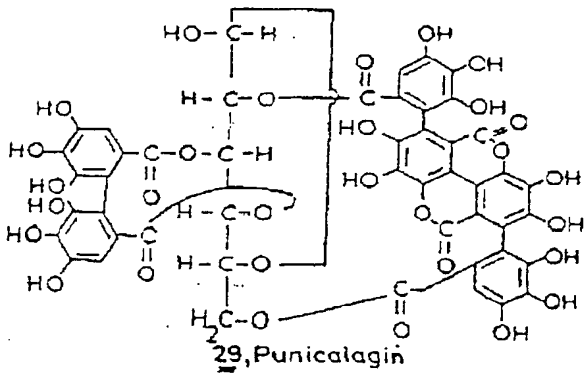
35, Eugenin



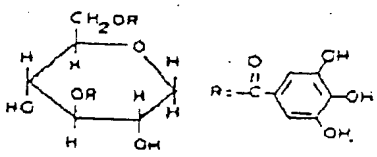
36, Hippomanin-A



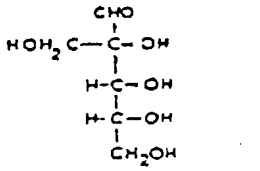
37, R_1=R_2=H



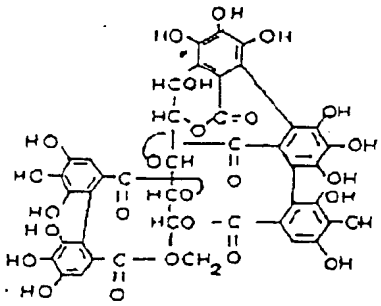
29, Punicalagin



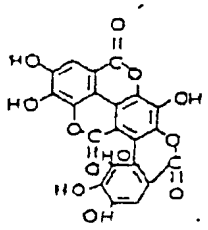
32, Aceritannin



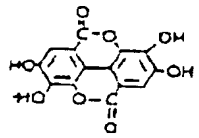
31, α-Oxymethyl -D-ribose



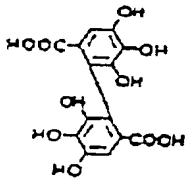
18, Castalagin

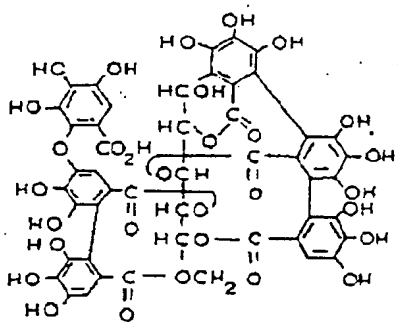


18a, Flavogallol

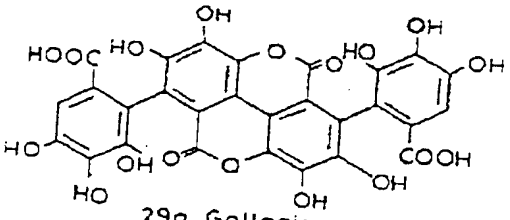


Ellagic acid

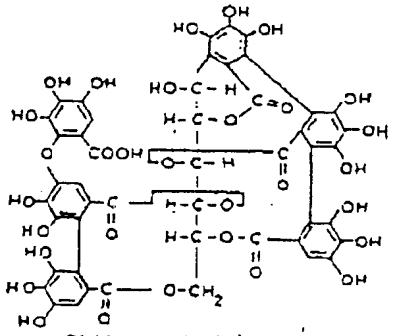




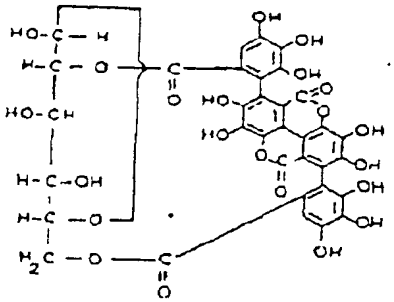
19, Castavaloninic acid



29a, Gallagic acid

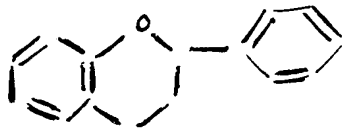


21, Vescavaloninic acid

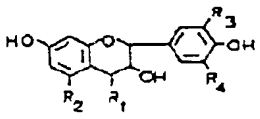


30, Punicalin

* condensed tannins, particularly tannins with formula



With two, preferably three hydroxyl groups



FLAVAN-3-ols (R_1=H)

a. ROBINETNIDOL, $R_1 = R_2 = H$; $R_3 = R_4 = OH$

b. GALLOCATECHIN, $R_1 = H$; $R_2 = R_3 = R_4 = OH$

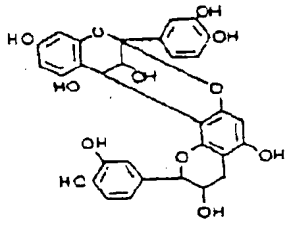
c. CATECHIN; $R_1 = R_4 = H$

$R_2 = R_3 = OH$

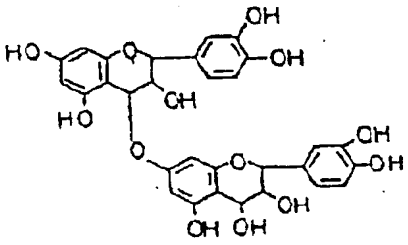
FLAVAN-3,4-DIOLS (R_1 = OH)

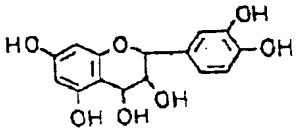
a. LEUCOROBINETINIDIN, $R_2 = H$; $R_1 = R_3 = R_4 = OH$

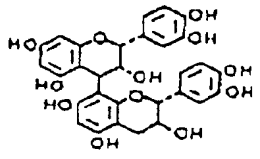
b. LEUCOFISETINIDIN, $R_2 = R_4 = H$; $R_1 = R_3 = OH$



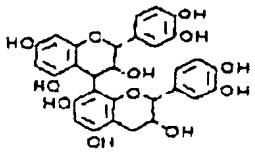
41 Procyanidin A



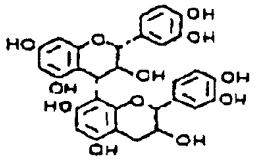




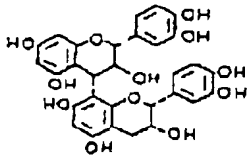
42a B1



42b B2

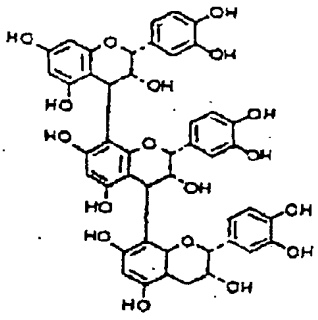


42c B3

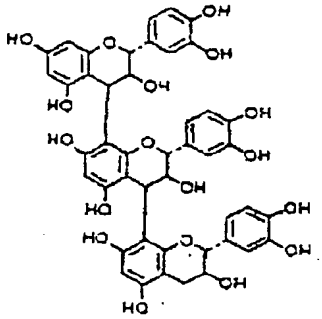


42d B4

Procyanidin Dimers

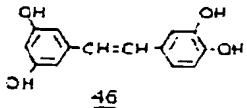


42e C1

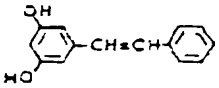


42f C2

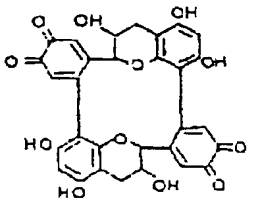
Procyanidin Trimers



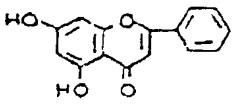
46



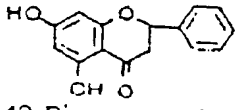
47 Pinosylvin



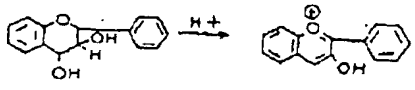
45 Head to tail Dimer of catechin



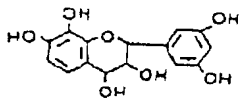
48,Chrysin



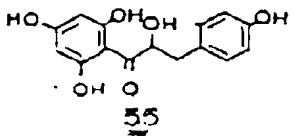
49,Pinocembrin



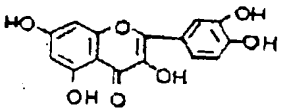
43 Leucoanthocyanidin Anthocyanidin



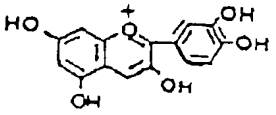
44,Melacacidin



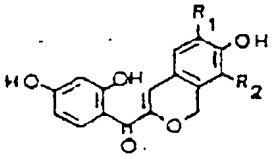
55



50, Quercetin

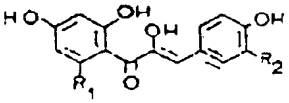


51, Cyanidin



56, R_1=H, R_2=OH

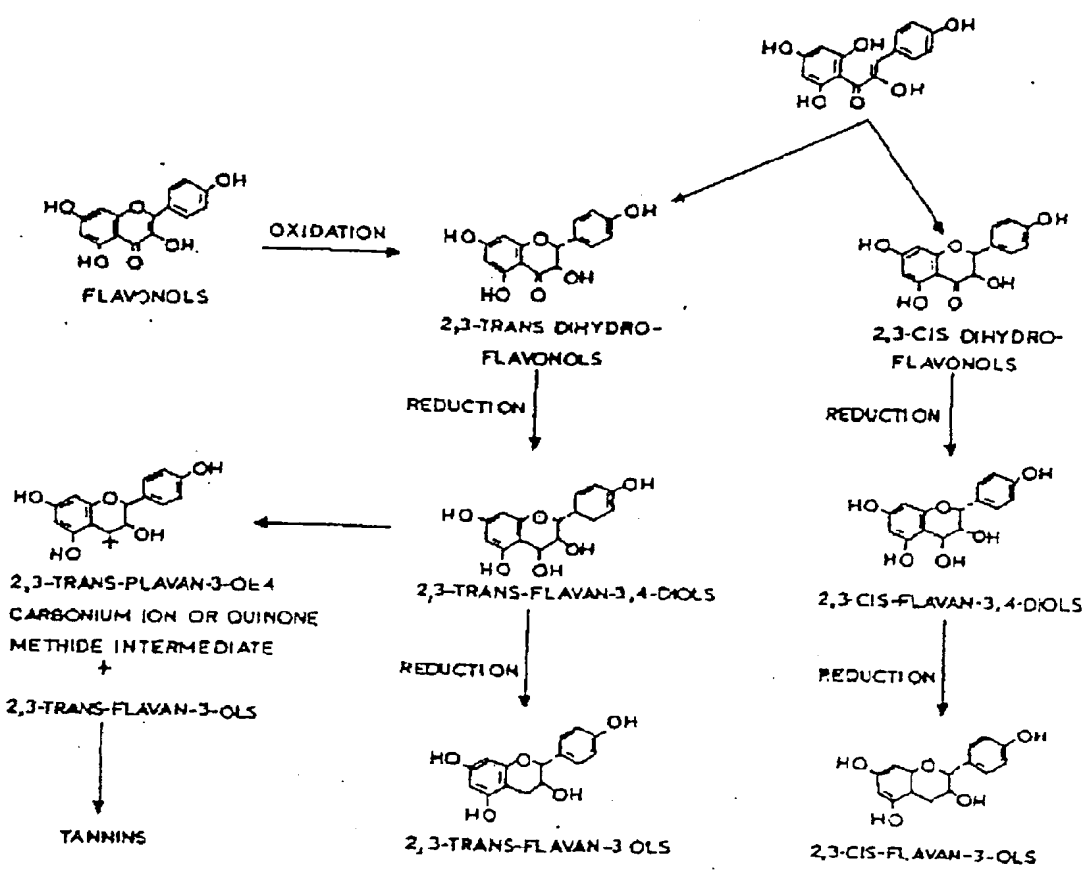
57, R_1=OH, R_2=H



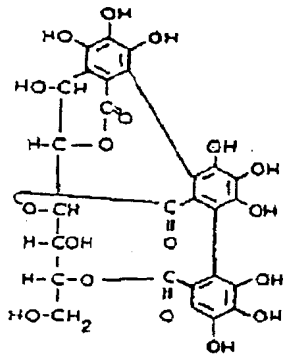
52, R_1=H, R_2=OH

53, R_1=OH, R_2=H

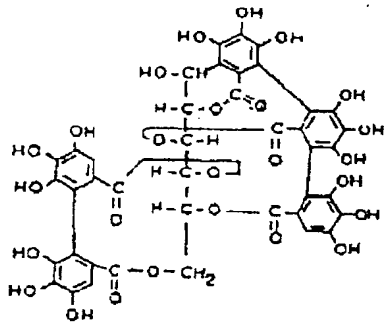
54, R_1=R_2=OH



* gallic acid
* digallic acid
* quinic acid
* 5-dehydroquinic acid
* shikimic acid
* 5-dehydroshikimic acid
* vescalin



* vascalagin



* salts and esters of these acids, particularly aliphatic, cycloaliphatic, aromatic, phosphoric esters, polyesters, etc.
* hydrolysis products of salts and esters of the above compounds, particularly aliphatic, cycloaliphatic, aromatic, phosphoric esters, polyesters, etc.
* condensation products of aldehyde, such as formaldehyde, glutaraldehyde, etc., with tannins, especially tannic acids of the general formula described hereabove

or with vescalin and/or vascalagin. Preferred

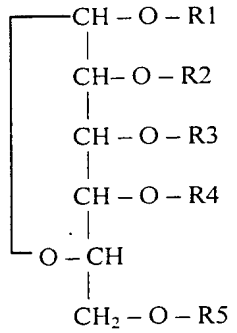
condensation products are condensation products of aldehyde, formaldehyde and/or glutaraldehyde with tannins, tannic acids, quinic acid, dehydroquinic acid, gallic acid, digallic acid, shikimic acid, dehydroshikimic acid, vescalin and/or vascalagin. Advantageously, at least two moles of tannins or tannic acids are used per mole of aldehyde. Preferably the aldehyde function of the aldehyde compounds are completely or substantially completely condensed with tannic acids or tannins.

The rest of gallic or digallic acid is intended as the radical obtained after removal of an OH group from the carboxylic function, i.e.

- $(CO)-(C_6H_5O_3)$ for gallic acid, and
- $(CO)-(C_6H_4O_2)-O-(CO)-(C_6H_5O_3)$ for digallic acid.

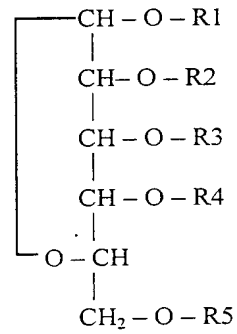
Preferably, in the cardiac valve according to the invention, the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising hydrolyzable tannins, salts of these acids, esters of these acids, hydrolysis products of said salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

More advantageously, the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising the tannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid (especially the tannins and tannic acids disclosed hereabove) and mixtures thereof.

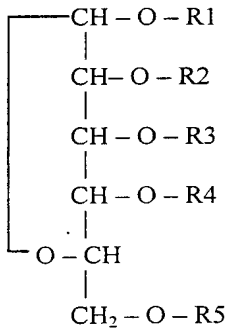
More advantageously, the cardiac valve according to the invention has, at its surface, an advantageously substantially continuous and substantially homogeneous layer, associated to or containing a compound selected from the group comprising tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or

digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid (preferably the tannins and tannic acids as listed hereabove) and mixtures thereof.

According to a particular embodiment, the valve has the form of a body associated, both at its surface and inside it, to one or more compounds selected from the group comprising acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

In the case of a biological tissue stabilized by an aldehyde, the latter allows to create bonds between the

collagen of the tissue and inside the tissue.

The invention also relates to the use of a body or tissue containing at least one biological compound and/or at least one polymer or copolymer compound and/or at least one partially cross-linked and biocompatible compound, said compound being associated at least partially to a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, for preparing an animal or human implant, particularly a cardiac implant, such as a cardiac valve, or vessels, ligaments, tendons, tracheas, membranes, esophagi, etc.

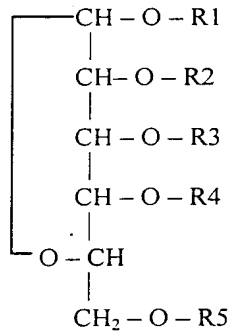
Advantageously, said compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is a compound as described hereinbefore as regards the cardiac valve according to the invention.

In accordance with a particular embodiment, the tissue in use is a biological tissue stabilized by an aldehyde, particularly by a glutaraldehyde, wherein the aldehyde (particularly the glutaraldehyde) at the surface of the tissue or in the proximity thereof is associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

Preferably, the biological tissue used as an implant is stabilized by an aldehyde associated to a compound as described hereinbefore as regards cardiac valves.

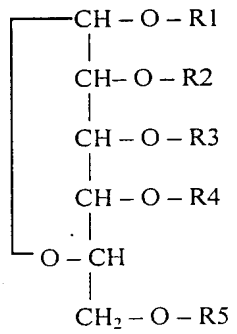
More advantageously, the tissue or body used as an implant is associated at least at its surface to a

compound selected from the group comprising the tannic acid with formula



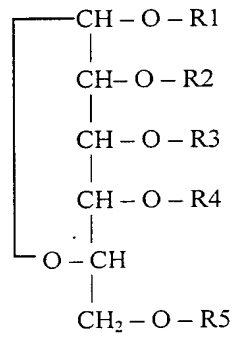
where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

More advantageously, the tissue or body, particularly the biological tissue used as an implant according to the invention has, at its surface, a substantially continuous and substantially homogeneous layer, containing or associated to one or more compounds selected from the group comprising tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid, and mixtures thereof.

According to a particular embodiment, the advantageously biological tissue used as an implant contains, both at its surface and inside it, a compound selected from the group comprising tannic acids with formula:



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of

quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.
In the case of a biological tissue, the presence of such a compound inside the body or tissue allows to create bonds between the collagen of the tissue and, for instance, aldehyde inside the tissue or body.

The invention further relates to a method for preparing a cardiac valve or a tissue or body used as an implant,

wherein this implant is treated with a solution containing a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, or wherein said implant is at least partially prepared from a polymer or copolymer compound or from a cross-linkable biocompatible compound at least partially treated or mixed with a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, and

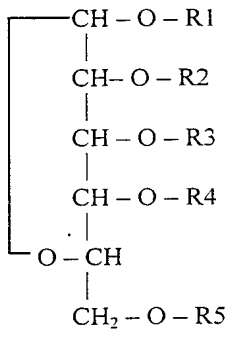
wherein, possibly after a rinsing and/or washing step, the implant is further sterilized and/or treated aseptically. Aseptic treatment of the implant is intended, amongst other things, as aseptic cleaning of an advantageously sterilized implant, rinsing with water, e.g. sterile water for injections, removal of fragments or residues of tissue in a sterile room, implant shaping, etc.

As compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, it is advantageous

to use a compound selected from the group comprising tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of dehydroshikimic acid, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

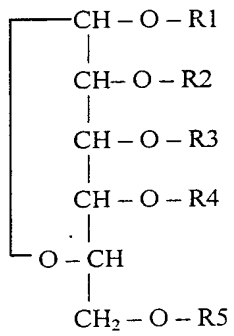
Preferably, as compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, a tannic acid, a salt of this acid, an ester of this acid, or a hydrolysis product of said salt or ester is selected.

Particularly, as a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, a compound is used which is selected from the group comprising: the tannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid, and mixtures thereof.

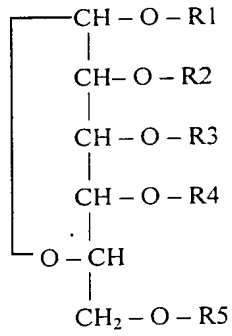
Advantageously, the treatment is carried out for obtaining, at the surface of the implant, a layer containing or associated to a compound selected from the group comprising: the tannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids and mixtures thereof.

Particularly, the treatment is carried out for obtaining an implant which contains both at its surface and inside its tissue, a compound selected from the

group comprising: the tannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids and mixtures thereof.

For instance, the implant is treated with a solution containing a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, and at least one solvent having at least one hydroxyl function, calcium-free water or water containing less than about 100 mg of calcium per liter.

According to an advantageous embodiment, the implant or tissue is treated with a solution containing a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, said solution having a pH of 3 to 9, particularly of 5.5 to 7.5. According to a possible embodiment, the content of compound(s) having

at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, is of 0.1 to 10% by weight, preferably of 0.5 to 5% by weight, particularly of 1 to 3% by weight. This treatment step is advantageously executed at a temperature below 25°C, e.g. a temperature of 0 to 25°C, advantageously at a temperature of 0 to 8°C, preferably at about 4°C.

After this treatment step, or during this treatment step, the implant or valve or tissue is advantageously submitted to a photooxidation step. Photooxidation is performed, for instance, by exposing the valve or tissue to the rays of a lamp, e.g. a halogen lamp or a lamp emitting to light with a wave length of 400 - 800 nano meter. This treatment step is possibly executed with oxygen being added, e.g. by bubbling the treatment solution with air. This photooxidation step seems to be useful to provide bonds between collagen molecules of the tissue and/or between collagen molecules and tannic acid. Irradiation may possibly occur after transplantation, e.g. by means of an endoscope.

When a tissue of biological origin is used, this tissue is advantageously stabilized by an aldehyde, particularly a glutaraldehyde. Stabilization is performed, for instance, by means of an advantageously aqueous solution containing 0.1 to 10% by weight, advantageously 0.2 to 5% by weight, preferably 0.3 to 1% by weight of aldehyde. Advantageously, aldehyde is glutaraldehyde. Stabilization advantageously occurs at a temperature below 25°C, e.g. a temperature of 0 to 25°C, advantageously a temperature of 0 to 8°C, preferably at about 4°C.

The implant so treated is advantageously aseptized and/or sterilized. Sterilization may be performed by immersion in a glutaraldehyde and/or formaldehyde

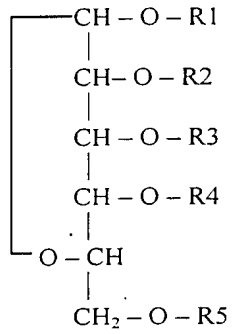
solution. For instance, sterilization is performed by means of an aqueous solution containing 0.6% by weight of glutaraldehyde, e.g. a solution buffered at a pH of 7 - 7.5. Sterilization is performed, for instance at a temperature of 0 to 50°C, particularly at a temperature of about 4°C, or at a temperature of about 37°C.

Sterilization may be performed by other treatments, e.g. gamma irradiation.

The invention further relates to a pharmaceutical preparation containing, as an agent against calcification, especially against calcification in a blood circuit, particularly of a cardiac valve (preferably according to the invention) and/or of an implant in contact with blood, an effective amount of at least one compound selected from the group comprising: tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of dehydroshikimic acid, and mixtures thereof. Such preparation also allows to prevent calcification in a blood circuit, particularly of a cardiac valve (preferably according to the invention) or of an implant in contact with blood.

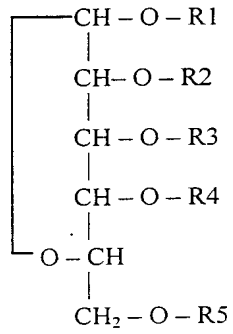
Advantageously, the preparation according to the invention contains, as an agent against calcification, particularly of a cardiac valve and/or of an implant in contact with blood, an effective amount of at least one

compound selected from the group comprising: the tannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, and mixtures thereof.

Preferably, the preparation contains, as an agent against calcification, an effective amount of at least one compound selected from the group comprising: tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids;

hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, and mixtures thereof.

Although the preparation according to the invention may be in the (intravenously) injectable form, e.g. of a blood bag, particularly containing a tannic acid, in the liquid or solid oral form, in the suppository form, in the form of a cream to be applied on the skin, or in the form of patches to be applied on the skin, oral forms are preferred. Among oral forms, long release preparations are preferred.

Solid oral forms are, for example, capsules, matrices, pellets, pastilles, chewing-gums, tablets, etc. These forms may be of the substantially immediate release type and/or of the substantially constant release type. In the case of matrices, matrices controlling the liberation or release of the active compound are advantageously used. In the case of capsules or pellets or tablets, coverings or coatings, advantageously a succession of coatings are advantageously used to control the release of the compound. Particularly, at least one coating is an enteric coating. For example, the active compound is mixed with a wetting agent and possibly with a pharmacological excipient, the active compound is then transformed into pellets, pastilles, granules, etc. said pellets, pastilles, granules, etc. being coated with a film, or a microporous membrane, containing, for instance, a pharmacological excipient, and a film forming mixture containing an acrylic and/or methacrylic polymer or copolymer which is insoluble in the organism and a polymer or non polymer substance (preferably a non acrylic and non methacrylic substance) which is insoluble in the acid gastric environment but is soluble in the intestine.

Solid oral forms contain, for instance, an unitary dose of 10 mg to 5 g, advantageously 20 mg to 1 g, preferably 50 mg to 500 mg of the active principle, or of a mixture of active principles, e.g. a dose of 100 mg, 200 mg, 250 mg, 400 mg.

The composition or preparation according to the invention is suitable, for instance, for patients who have had a cardiac valve transplant, particularly involving the cardiac valve according to the invention.

The composition or preparation according to the invention may also be administered to an animal, e.g. a pig, whose pericardium is to be removed to make cardiac valves for transplantation.

The composition or preparation according to the invention, said composition containing possibly further active agent(s), is also suitable for treating or preventing diseases involving calcification, such as urolethiasis, artherosclerosis, hydatic diseases of the liver, cerebral or brain calcification, rheumatoïd arthritis, SLE (systemic lupus erythematosus), calcinosis of the hand, carcinome, arterial plaque, tumor calcification, Dystrophic calcification, dental plaque, calculus and other diseases involving calcification which are listed in Arch Pathol Lab Med, Vol 107, July 1983, Calcific Diseases A concept by Anderson, pages 341 to 347, the content of which is incorporated by reference.

The composition or preparation of the invention is also suitable in the treatment of calculus, such as kidney calculus, urether calculus, etc. by means of ultrasound(s) or litotripsis. The composition or preparation is given to a patient before his treatment by ultrasound(s) or litotripsis, so that the treatment

has to be less severe. The invention relates thus also to a method of treatment of a patient suffering a calculus, in which an efficient amount of composition or preparation of the invention is administered to the patient before his treatment with ultrasound(s). For example, during a few days, preferably at least one week before the treatment with ultrasound(s), the patient receives several doses of the composition or preparation of the invention. After such a treatment, the preparation or composition is advantageously administered for preventing or reducing the formation of calculus.

The composition or preparation of the invention can also take the form of a tooth pasta and/or buccal solution, such as a rinsing buccal solution.

The composition or preparation according to the invention may also contain one or more further supplementary active principles. For example, the solid oral form may contain an agent against cholesterol ,particularly Zocor, Mevacor, a mixture of campestanol and sitostanol, etc.

The invention relates also to a support intended to be in contact with a biological medium, especially with a human or animal medium, such as an implantable support, advantageously of a biological implantable support and/or an implantable support containing a polymer or copolymer compound, and/or an implantable support containing an at least partly cross-linked and biocompatible compound, said support being associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

Examples of such support are: artificial heart or part thereof, artificial kidney or part thereof, pumps, micro pumps, insulin delivering pumps, bioreactors,

stents, catheters, tubes, artificial veins, valves, polyurethane valves, sensors, fibrin membrane, power cells, pace makers, identification chips such as for dogs, chargers of power cells, and any other devices intended to be in contact with a biological medium, such as a biological fluid.

Advantageously, the support of the invention has, at least at one of its surface, one or more compounds having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, said compound/s being advantageously associated to the polymer or copolymer compound or to the at least partially cross-linked biocompatible compound.

Preferably, the support has the form of a biological tissue, stabilized at least partially by a polymer, copolymer or an at least partially cross-linked biocompatible compound, associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

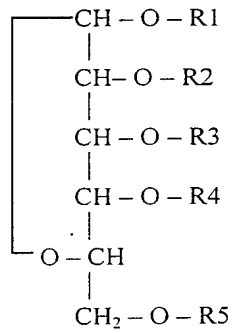
For example, the biological tissue is stabilized at least partially by an aldehyde, the aldehyde which is at least at the surface of the tissue or in the proximity thereof being at least partially associated to a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

Preferably, the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, is selected from the group comprising tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid,

hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of dehydroshikimic acid, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid, and mixtures thereof.

Most preferably, the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising hydrolyzable tannic acids, salts of these acids, esters of these acids, hydrolysis products of said salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid, and mixtures thereof.

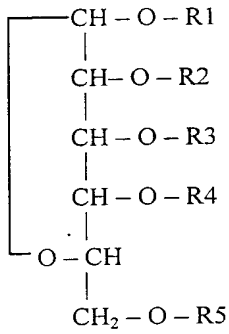
Typically, the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising the tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of

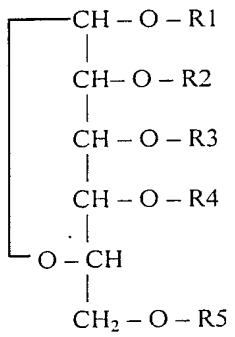
quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

According to an embodiment, the support has, at its surface in contact with the biological medium, a layer containing at least one compound selected from the group comprising tannic acids with formula



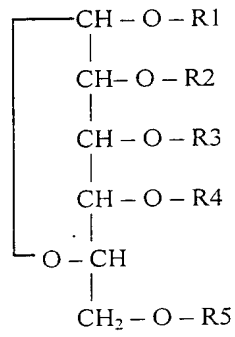
where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof.

However, preferably, the support has the form of a body having, both at its surface and inside it, a compound selected from the group comprising compounds with formula



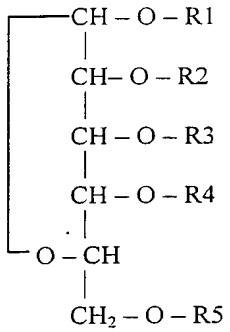
where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof.

Still a further subject matter of the invention, is an aqueous stabilizing composition for a support selected from the group consisting of support to be in contact with a biological medium (such as a biological fluid, for example blood), implantable support, biological support, animal tissue, and human tissue, said composition containing:- at least an aldehyde in mixture with a compound selected from the group comprising compounds with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof, or

- a compound selected from the group comprising compounds with formula

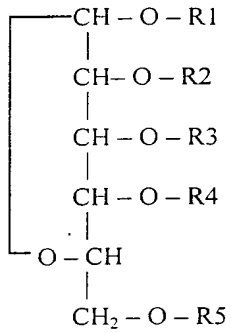


where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, in mixture with a condensation product of an aldehyde with the above mentioned tannins or tannic acids.

Advantageously, the pH of the composition is comprised between 3 to 9, advantageously between 5.5 and 7.5, preferably about 7.

According to an embodiment, the composition

contains up to 10%, advantageously less than 5%, preferably less than 2.5% by weight of a first compound selected from the group comprising compounds with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, and mixtures thereof, and up to 10%, advantageously less than 5%, preferably less than 2.5% by weight of an aldehyde and/or a condensation product of an aldehyde with said tannins or tannic acids.

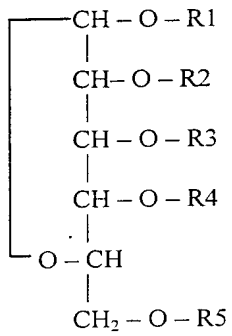
Preferably, the composition contains a phosphate buffer.

In the stabilizing composition of the invention, the weight ratio first compound/aldehyde is advantageously comprised between 1:10 and 10:1, preferably 1:5 and 5:1.

The stabilizing composition of the invention can be a ready-to-use composition, but is preferably marketed as a kit comprising a first vial containing the first compound as an aqueous solution, but preferably in the

form of a powder, said first vial being substantially free of aldehyde, and a second vial containing an aqueous solution containing aldehyde (said vial being free or substantially free of tannic acid or tannin), the content of the said two vials having to be mixed together so as to prepare the stabilizing composition. Advantageously the second vial contains at least partly the phosphate buffer. The water used is advantageously sterile water, preferably pyrogen free water.

The kit of the invention for preparing a stabilizing composition of the invention comprises advantageously a first bottle containing, as a powder or in an aqueous solution (preferably as a powder), a first compound selected from the group comprising compounds with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, (said first vial being preferably free or substantially free of aldehyde) and

a second bottle containing an aqueous solution containing an aldehyde and preferably a phosphate buffer (said solution being preferably free or substantially

free of the said first compound), the content of the said bottles having to be mixed together for preparing the stabilizing solution.

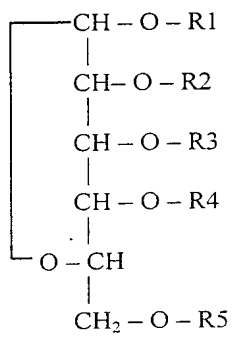
Further details and characteristics of the invention will appear from the following detailed description of particular embodiments, which are described by way of example only.

In this description, reference is made to the annexed drawings. In these drawings,

- figure 1 shows a bovine pericardium treated with a glutaraldehyde solution (without tannic acid) after an incubation in a phosphate buffer containing 2.2mM $CaCl_2$ for 5 weeks,
- figure 2 shows the calcium dosage after incubation for 8 weeks for different treated tissues, and
- figure 3 shows the calcium dosage after incubation for 9 weeks for different treated tissues.

After removal, the pericardium or valve of the pig was rinsed out with an isotonic saline solution. Then, it was cut up into several pieces of tissues.

Glutaraldehyde aqueous solutions were prepared by diluting a concentrated glutaraldehyde solution through the addition of demineralized water thereto, by using a phosphate aqueous buffer solution (sodium phosphate buffer - pH 7.4), and by adding, if need be, gallotannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid - (CO)-($C_6H_5O_3$)

(Reference) tissue 1.
This tissue was treated in an aqueous solution buffered with a phosphate buffer with 0.6% by weight glutaraldehyde (pH of the solution: about 7) for 24 hours at 4°C.

(Reference) tissue 2.
These tissues were treated in an aqueous solution buffered with a phosphate buffer with 2.0% by weight glutaraldehyde (pH of the solution about 7) for 24 hours at 4°C.

Tissue 3.
This tissue was treated in an aqueous solution buffered with a phosphate buffer with 0.6% by weight glutaraldehyde (pH of the solution about 7) for 24 hours at 4°C, before treatment in a solution containing 1% by weight of gallotannic acid (in presence of a phosphate buffer, pH of about 7) for 8 hours at 4°C.

Tissue 4.
This tissue was treated in an aqueous solution containing 0.6% by weight glutaraldehyde and 1.0% by weight gallotannic acid (in presence of a phosphate buffer, pH of the solution about 7) for 24 hours at 4°C.

Tissue 5.
This tissue was treated in an aqueous solution containing 2% by weight glutaraldehyde and 1.0% by weight gallotannic acid (in presence of a phosphate buffer, pH of the solution about 7) for 24 hours at 4°C.

Tissue 6.
This tissue was treated in an aqueous solution containing 1.0% by weight gallotannic acid (in presence of a phosphate buffer, pH of the solution about 7) for 24 hours at 4°C.

After treatment, tissues 1 to 6 were rinsed out

with a NaCl solution in sterile physiological demineralized water (physiological saline solution). Tissues were further sterilized by immersion in a 0.6% glutaraldehyde buffer solution for 48 hours at 37°C.

Determination of in vitro calcification of treated and sterilized tissues.

After treatment, these tissues were placed in Petri dishes containing a solution with 135 millimole of NaCl per liter, 2.2 millimole of $CaCl_2 2H_2O$ per liter, 1.2 millimole of KH_2PO_4 per liter, and 0.05 millimole of 3-(N-morpholino-propane) sulfonic acid, this solution being buffered at pH 7.4 by means of a phosphate buffer and being sterilized by laminar flow filtration.

Petri dishes are placed in an incubator at 37°C, in a CO_2 atmosphere for 35 days, the solutions in the dishes being refreshed every 7 days under sterile conditions.

The calcification rate of tissues after incubation in the Petri dishes was first determined by examination by a scanning electron microscope provided with an X-ray detector, and by flame emission spectrophotometry through atom absorption.

In order to allow an X-ray examination by scanning electron microscopy, parts of the treated tissues were fastened to an aluminum support, covered by carbon particles of less than 10 nanometers in argon for 60 seconds, and then analyzed by a Philips XL 20 scanning microscope, provided with a ray detector EDAX. This analysis allows to identify and quantify the presence of elements such as calcium and phosphor at the surface of the tissue under examination.

For the spectrophotometric examination, parts of the treated tissues were washed with a sterile saline solution and dried at 90°C in a dessicator. After digestion in a 70% nitric acid solution (3 parts by weight), the calcium content was further determined by flame spectrophotometry (Perkin Elmer device, Zeeman

5100 type).

The preservation of the tissues according to the invention was analyzed by a transmission electron microscope. In order to allow transmission electron microscopic examination, parts of the treated tissues are dehydrated to obtain resin blocks. These blocks are further cut up into extra-thin slices, which are collected in a copper dish, where they are treated with a saturated solution of uranyl alcohol acetate and of lead citrate. Then, the slices were examined by a scanning and transmission electron microscope (Philips EM 300 G).

These examinations showed that the tissues 3 to 6 according to the invention had a lower calcification than reference tissues 1, 2 and that the ultra structure of the tissues 3, 4, 5 and 6 according to the invention was better maintained. Tissues 3, 4, 5, 6 had the lowest calcification and a structure substantially corresponding to the ultra structure of the fresh non-treated tissue.

Figure 2 is a graph showing the calcium dosage measured after an incubation of 8 weeks for the tissues 2, 5 and 6. As it can be seen from said graph the calcification of the tissues 5 and 6 was well below 10µg/mg of dry tissue, i.e. more than about 15 times lower than the calcification of the tissue 2.

Figure 3 is a graph showing the calcium dosage measured after an incubation of 9 weeks for the tissues 1, 4, 2 and 5. As it can be seen from said graph the calcification of the tissues 3 and 5 was well below 10µg/mg of dry tissue, i.e. more than about 10 times less than the calcification of the tissue 1 or 2.

It is worthwhile to note that the calcification rate of a tissue treated only by means of glutaraldehyde can vary of more than about 50µg/mg dry tissue for a period of 8 weeks (variation from about 80 to about 140 µg/mg dry tissue), while for tissues according to the

invention the calcification rate of a tissue is in any case less than 10µg/mg of dry tissue for a period of 8 weeks.

Determination of in vivo calcification of treated and sterilized tissues.

In vivo determination was carried out by using rats weighing 200 grams. Each animal received in its dorsal part (cranial part and caudal part), in four distinct subcutaneous pockets two pieces of tissue 6, and two pieces of tissue 1 as reference. After placing the tissue in a pocket, the pocket was closed by means of a suture material Dermalon 2.0, by a needle CE-6 (sold by Cyanamide Bénélux).

The rats were fed with laboratory rat food (Purina Meals Inc.). 21 days after tissue implantation, the rats were killed by a lethal dose of thiopental (300 mg/kg) before getting the samples of implanted tissues from the rats.

As for the in vitro tests, the samples of implanted tissues were submitted to visual examination, to a transmission and scanning electron microscope examination, and to a flame spectrophotometric examination by atom absorption.

This examination showed that tissues 3, 4, 5 and 6 had a lower calcification than the reference tissues 1 and 2.

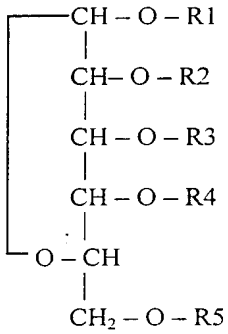
Parts of tissue 3 and parts of tissue 4 were submitted, before being sterilized with formaldehyde, to halogen lamp irradiation. In this treatment step, the parts of tissues 2 and 3 were immersed in sterile water having a pH of 7.4 and a temperature of about 20°C. The irradiation lasted 48 hours and was performed with an intensity of about 400-600 lumen/hour.

After irradiation, said parts of tissue were rinsed out with sterile injectable water and exposed to gamma irradiation.

Preparations according to the invention will be described hereafter:

Example of liquid oral preparation.

200 mg of gallotannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid -(CO)-($C_6H_5O_3$), were dissolved in 100 ml of water containing 1 gram of taste-masking aspartame.

Examples of solid oral form.

Example 1

The following ingredients were used to make microgranules:

Gallotannic acid (same formula as oral form): 50 g

Sucroester WE 15 (Gattefosse): 100 g

Avicel PH 101 (FMC microcrystalline cellulose): 100 g

Polyvinyl pyrrolidone K 30: 10 g

These ingredients were put in powder form, into a planetary mixer and granulated by addition of 100 g of distilled water- The plastic mass so obtained was extruded through the cylindrical die, with a diameter of 1 mm, of an extruder (Alexanderwerk). The cylinders so obtained were further transformed into spheres by

spheronization in a device of the Maumerizer type. After being dried for 24 hours in a ventilated room, at 50°C, the fraction of microgranules having a diameter of 0.7 to 1.4 mm was separated by screening.

Microgranules (0.7 mm - 1.4 mm) were coated with a porous membrane by spraying thereon, in a fluid bed (Aeromatic, Strea type) a dispersion, composed of:

Talc (lubricant): 5 parts by weight

Polyvinyl pyrrolidone (plasticizer): 0.75 parts by weight

Tween 20 (wetting agent): 0.05 parts by weight

Hydroxypropylmethyl cellulose phatalate HP 55 F (enteric chemical): 7 parts by weight

Eudragit E30D (insoluble polymer): 41 parts by weight

Distilled water: 46 parts by weight

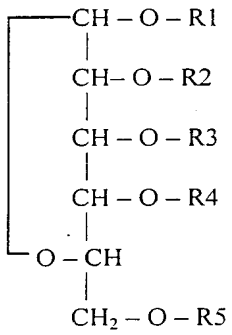
This dispersion was sprayed on the microgranules in the amount of 1 part by weight of dispersion per 2 parts by weight of microgranules. Then, the coated microgranules were dried in an oven at 50°C for 24 hours.

Microganules so obtained, possibly mixed with sucrose granules, were inserted in gelatin capsules. So, capsules containing 200 mg of gallotannic acid (each capsule containing 1.5 g of coated microgranules and 1.5 g of sucrose granules) and capsules containing 400 mg of gallotannic acid (each capsule containing 3 g of coated microgranules) were prepared.

Thanks to their particular porous membrane, the microgranules had prolonged release or liberation properties.

Example 2

Example 1 has been repeated, except that gallotannic acid of formula 200 mg of gallotannic acid with formula



where R1, R2, R3, R4 and R5: the rest of digallic acid, namely - (CO)-($C_6H_4O_2$)-O-(CO)-($C_6H_5O_3$).

Example 3

Example 1 has been repeated, except that a mixture of gallotannic acids was used, said mixture containing 50% by weight of the gallotannic acid of example 1 and 50% by weight of the gallotannic acid of example 2.

Example 4

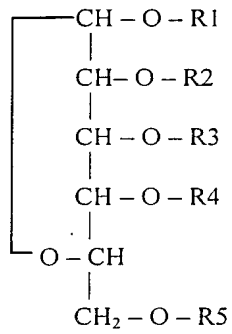
Example 1 has been repeated, except that vascalagin was used as tannic acid.

Example 5

Example 1 has been repeated, except that vescalin was used as tannic acid.

Example of a stabilizing solution

The solution was prepared by mixing the content of a first vial or bottle with the content of a second vial or bottle, the first vial containing 1 g of gallotannic acid of formula



where R1, R2, R3, R4 and R5: the rest of digallic acid, namely - $(CO)-(C_6H_4O_2)-O-(CO)-(C_6H_5O_3)$,
while the second vial contains 100ml of an aqueous solution (prepared by using sterile pyrogen free water) containing 1% by weight glutaraldehyde and a sufficient amount of phosphate buffer (sodium phosphate buffer) so as to obtain after mixing the content of the two vials a solution having a pH of about 7.

The mixing of the content of the two vials can be effected by adding the content of the first vial into the second vial. However, preferably the content of the second vial is introduced in the first vial for rehydration of the gallotanic acid, said hydration step being advantageously carried out at a temperature of 20-50°C, preferably at about 37°C. The complete hydration of the gallotannic acid was obtained in the present case after 15 minutes at 37°C. Preferably, the content of the two vials is shaked.

CLAIMS.

1. A cardiac valve which has a biological or biocompatible support associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

2. A cardiac valve as claimed in claim 1, characterized in that it is at least partially made from a polymer or copolymer compound or an at least partly cross-linked and biocompatible compound, associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

3. A cardiac valve as claimed in claim 1 or 2, characterized in that the biological or biocompatible support has, at least at its surface, one or more compounds having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

4. A cardiac valve as claimed in claims 2 and 3, characterized in that the biological or biocompatible support has, at least at its surface, one or more compounds having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, which are associated to the polymer or copolymer compound or to the at least partially cross-linked and biocompatible compound.

5. A cardiac valve as claimed in any claim 1 to 4, characterized in that it has the form of a biological tissue, stabilized at least partially by a polymer or copolymer compound or by an at least partially cross-linked and biocompatible compound, associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

6. A cardiac valve as claimed in claim 5,

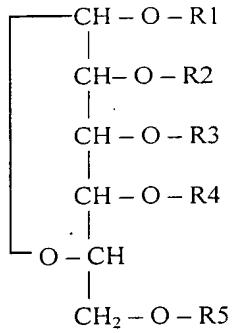
characterized in that the biological tissue is stabilized at least partially by an aldehyde, the aldehyde at the surface of the tissue or in the proximity thereof being at least partially associated to a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

7. A cardiac valve as claimed in any claim 1 to 6, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, is selected from the group comprising tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of dehydroshikimic acid, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

8. A cardiac valve as claimed in claim 7, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising tannic acids, salts of these acids, esters of these acids, hydrolysis products of said salts and esters, and mixtures thereof.

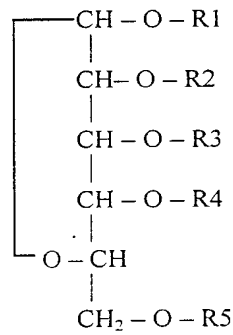
9. A cardiac valve as claimed in claim 7, characterized in that the compound having at least one

ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising the tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

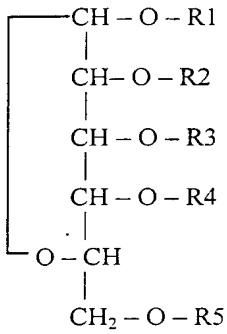
10. A cardiac valve as claimed in any preceding claim, characterized in that, at its surface, it has a layer containing at least one compound selected from the group comprising tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or

digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

11. A cardiac valve as claimed in any preceding claim, characterized in that it has the form of a body having, both at its surface and inside the body, one or more compounds selected from the group comprising acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

12. A use of a support, advantageously of a biological support and/or a support containing a polymer or copolymer compound, and/or a support containing an at least partly cross-linked and biocompatible compound,

said support being associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, for preparing an animal or human implant, particularly a cardiac valve.

13. A use as claimed in claim 12, characterized in that the implant has, at least at its surface, one or more compounds having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, said compound/s being advantageously associated to the polymer or copolymer compound or to the at least partially cross-linked biocompatible compound.

14. A use as claimed in claim 12 or 13, characterized in that the implant has the form of a biological tissue, stabilized at least partially by a polymer, copolymer or at least partially cross-linked biocompatible compound, associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

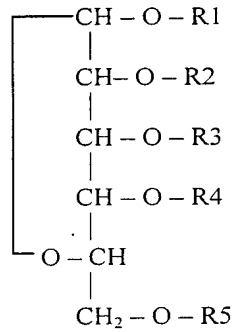
15. A use as claimed in claim 14, characterized in that the biological tissue is stabilized at least partially by an aldehyde, the aldehyde which is at least at the surface of the tissue or in the proximity thereof being at least partially associated to a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

16. A use as claimed in any claim 12 to 15, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, is selected from the group comprising tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid,

esters and salts of quinic acid and of dehydroquinic acid, hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of dehydroshikimic acid, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid, and mixtures thereof.

17. A use as claimed in claim 16, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising hydrolyzable tannic acids, salts of these acids, esters of these acids, hydrolysis products of said salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid, and mixtures thereof.

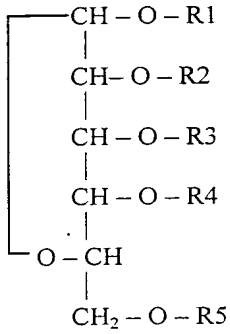
18. A use as claimed in claim 17, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising the tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or

digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

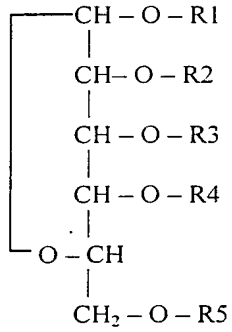
19. A use as claimed in any claim 12 to 18, characterized in that, at its surface, it has a layer containing at least one compound selected from the group comprising tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof.

20. A use as claimed in any claim 12 to 19, characterized in that the implant has the form of a body having, both at its surface and inside it, a compound

selected from the group comprising compounds with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof.

21. A method for preparing an animal or human implant, comprising a support, advantageously a support associated to at least a polymer or copolymer compound, or to a partially cross-linked biocompatible compound, wherein this implant is treated with a solution containing a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, or wherein said implant is at least partially prepared from a polymer or copolymer compound or from a cross-linkable biocompatible compound at least partially treated with a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, and
wherein, following said treatment, said implant is sterilized and/or treated aseptically.

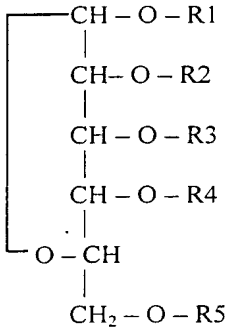
22. A method as claimed in claim 21, characterized

in that, as an implant, a biological tissue is used, which is stabilized at least partially by an aldehyde.

23. A method as claimed in claim 21 or 22, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, is selected from the group comprising tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of dehydroshikimic acid, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids and mixtures thereof.

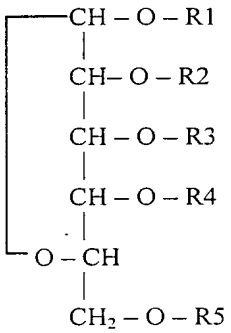
24. A method as claimed in claim 23, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising tannic acids, salts of these acids, esters of these acids, hydrolysis products of said salts and esters, and mixtures thereof.

25. A method as claimed in claim 24, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, is selected from the group comprising the tannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof.

26. A method as claimed in any claim 21 to 25, characterized in that the implant is treated with a solution containing a compound selected from the group comprising tannic acids with formula



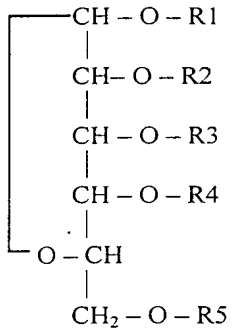
where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids;

quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids and mixtures thereof.

27. A method as claimed in any claim 21 to 26, characterized in that the implant is treated with a solution containing a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, said solution having a pH of 3 to 9, particularly of 5.5 to 7.5.

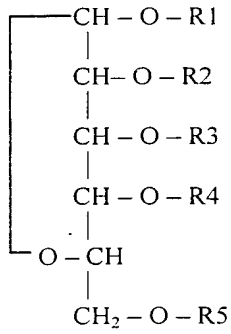
28. Pharmaceutical preparation containing, as an agent against calcification, especially in a blood circuit, particularly against calcification of a cardiac valve and of an implant in contact with blood, an effective amount of at least one compound selected from the group comprising: tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of dehydroshikimic acid, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

29. A pharmaceutical preparation as claimed in claim 28, characterized in that it contains, as an agent against calcification of a cardiac valve and of an implant in contact with blood, an effective amount of at least one compound selected from the group comprising: the tannic acid with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids and mixtures thereof.

30. A preparation as claimed in claim 28, characterized in that it contains, as an agent against calcification, an effective amount of at least one compound selected from the group comprising: tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; hydrolysis products of these salts and esters vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

31. A preparation as claimed in any claim 28 to 30, characterized in that it has the form of a prolonged release preparation.

32. Support intended to be in contact with a biological medium, especially with a human or animal medium, such as implantable support, advantageously of a biological implantable support and/or an implantable support containing a polymer or copolymer compound, and/or an implantable support containing an at least partly cross-linked and biocompatible compound, said support being associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

33. The support of claim 32, characterized in that the support has, at least at one of its surface, one or

more compounds having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, said compound/s being advantageously associated to the polymer or copolymer compound or to the at least partially cross-linked biocompatible compound.

34. The support of claim 32 or 33, characterized in that the support has the form of a biological tissue, stabilized at least partially by a polymer, copolymer or an at least partially cross-linked biocompatible compound, associated to at least one compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

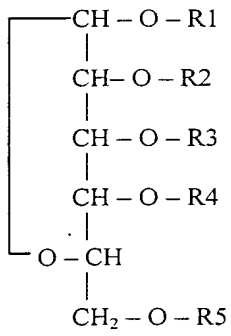
35. The support of claim 34, characterized in that the biological tissue is stabilized at least partially by an aldehyde, the aldehyde which is at least at the surface of the tissue or in the proximity thereof being at least partially associated to a compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon.

36. The support of claim 32 to 35, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon, is selected from the group comprising tannins, tannic acids, salts of tannic acids, esters of tannic acids, hydrolysis products of salts and esters of tannic acids and tannins, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, hydrolysis products of esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of esters and salts of gallic acid and of digallic acid, shikimic acid, dehydroshikimic acid, salts and esters of shikimic acid and of

dehydroshikimic acid, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid, and mixtures thereof.

37. The support of claim 36, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising hydrolyzable tannic acids, salts of these acids, esters of these acids, hydrolysis products of said salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid, and mixtures thereof.

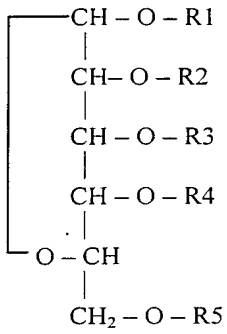
38. The support of claim 37, characterized in that the compound having at least one ring of 6 carbon atoms with at least two hydroxyl groups, preferably at least three hydroxyl groups thereon is selected from the group comprising the tannic acids with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of esters and salts of these acids, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of

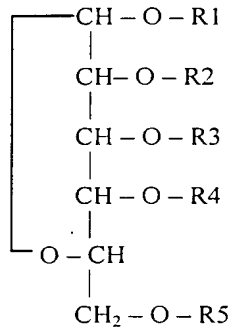
vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acid and mixtures thereof.

39. The support as claimed in any claims 32 to 38, characterized in that, at its surface, it has a layer containing at least one compound selected from the group comprising tannic acids with formula



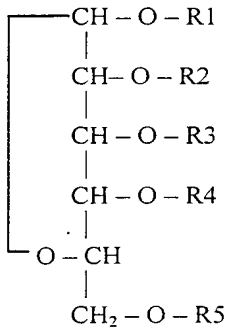
where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid; salts and esters of these tannic acids; quinic acid; dehydroquinic acid; esters and salts of quinic acid and of dehydroquinic acid; gallic acid; digallic acid; esters and salts of gallic acid and of digallic acid; hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof.

40. The support as claimed in any claims 32 to 39, characterized in that the implant has the form of a body having, both at its surface and inside it, a compound selected from the group comprising compounds with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof.

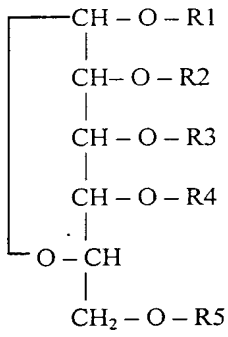
41. An aqueous stabilizing composition for a support selected from the group consisting of support intended to be in contact with a biological medium, implantable support, biological support, animal tissue, and human tissue, said composition containing:- at least an aldehyde in mixture with a compound selected from the group comprising compounds with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids,

quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, condensation product of an aldehyde with said tannins or tannic acids, and mixtures thereof, or

- a compound selected from the group comprising compounds with formula

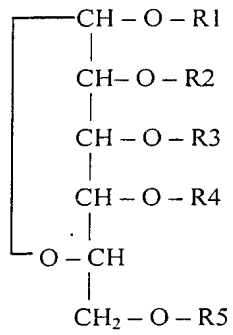


where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, in mixture with a condensation product of an aldehyde with the above mentioned tannins or tannic acids.

42. The composition of claim 41, characterized in that the pH of the composition is comprised between 3 to 9, advantageously between 5.5 and 7.5, preferably about 7.

43. The composition of claim 41 or 42, characterized in that it contains up to 10%,

advantageously less than 5%, preferably less than 2.5% by weight of a first compound selected from the group comprising compounds with formula

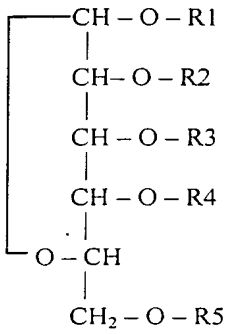


where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, and mixtures thereof, and up to 10%, advantageously less than 5%, preferably less than 2.5% by weight of an aldehyde and/or a condensation product of an aldehyde with said tannins or tannic acids.

44. The composition of any one of the claims 41 to 43, characterized in that it contains a phosphate buffer.

45. The composition of claim 43, characterized in that the weight ratio first compound/aldehyde is comprised between 1:10 and 10:1, advantageously 1:5 and 5:1.

46. A kit for preparing a composition of any one of the preceding claims 41 to 45, said kit comprising a first bottle containing, as a powder or in an aqueous solution, a compound selected from the group comprising compounds with formula



where R1, R2, R3, R4 and R5: the rest of gallic acid or digallic acid, salts and esters of these tannic acids, quinic acid, dehydroquinic acid, esters and salts of quinic acid and of dehydroquinic acid, gallic acid, digallic acid, esters and salts of gallic acid and of digallic acid, hydrolysis products of these salts and esters, vescalin, vascalagin, hydrolysis products of vescalin or vascalagin, esters and salts of vescalin and vascalagin, and

a second bottle containing an aqueous solution containing an aldehyde and preferably a phosphate buffer, the content of the said bottles having to be mixed together for preparing the stabilizing solution.

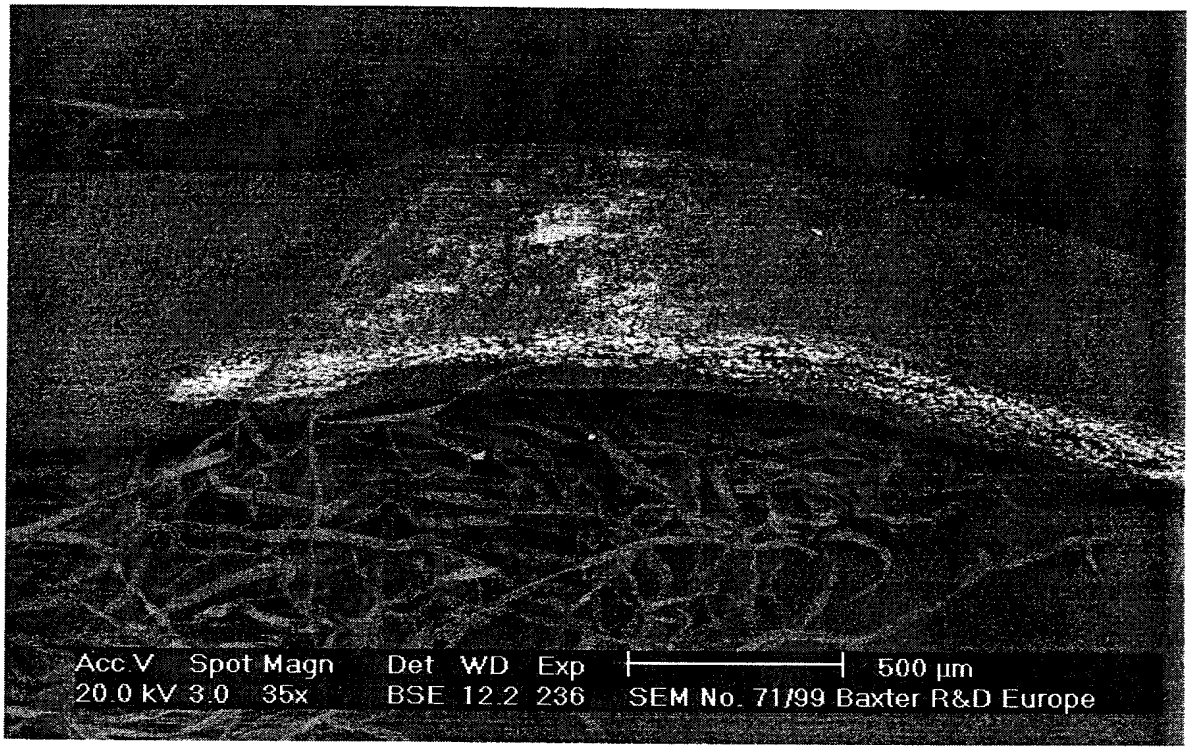

Acc.V Spot Magn Det WD Exp 500 µm
20.0 kV 3.0 35x BSE 12.2 236 SEM No. 71/99 Baxter R&D Europe

Figure 1

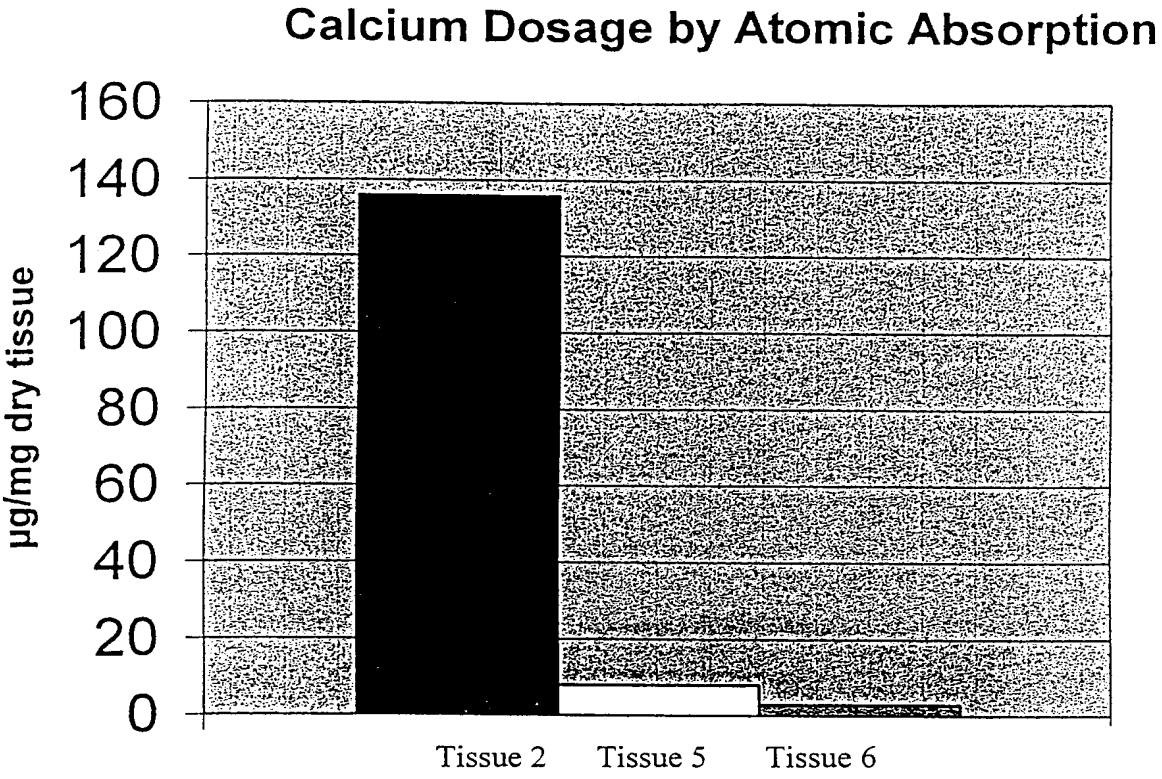


Figure 2

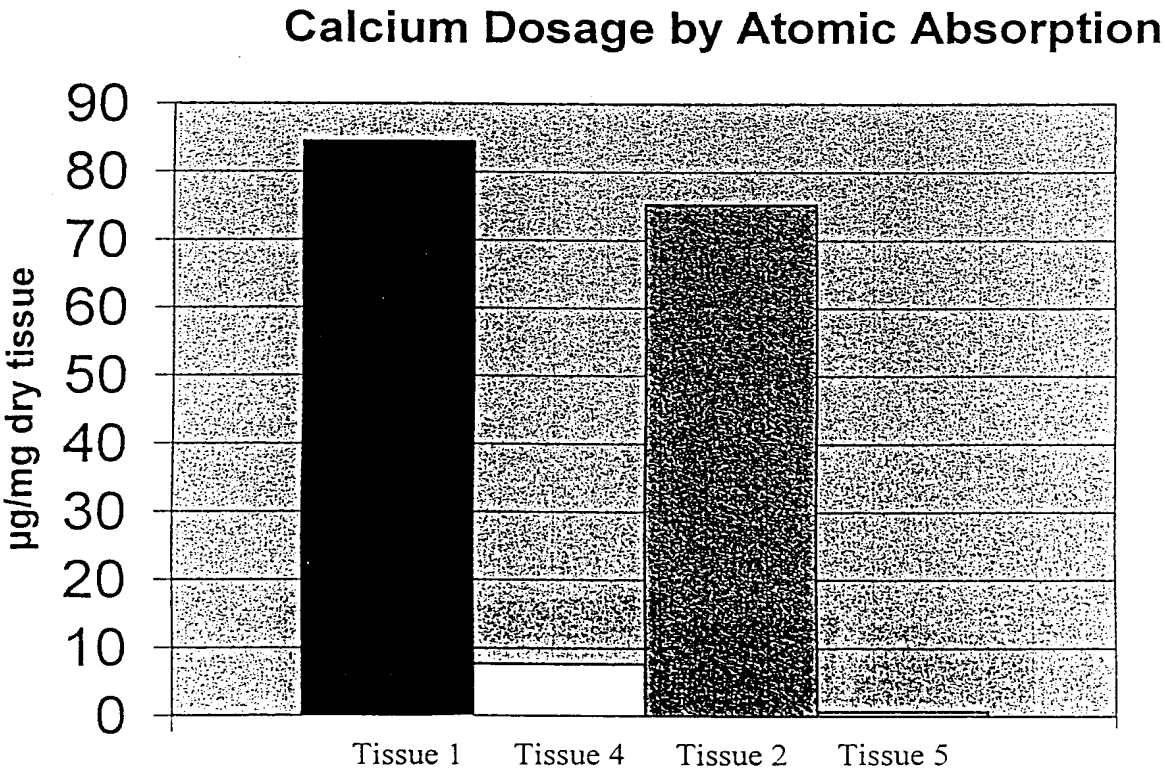


Figure 3

INTERNATIONAL SEARCH REPORT

Intern...onal Application No
PCT/BE 99/00121

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/54 A61K31/19 A61K31/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 01, 29 January 1999 (1999-01-29) & JP 10 262564 A (SAKAI SANGYO KK), 6 October 1998 (1998-10-06)	28-31
Y	abstract	1-27
X	WO 92 19597 A (MEDEA RES SRL) 12 November 1992 (1992-11-12) page 2, line 2 - line 8	28
X	US 5 843 471 A (CHAYKIN STERLING) 1 December 1998 (1998-12-01) column 1, line 66 -column 2, line 25	28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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31 May 2000	09/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Diederen, J

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INTERNATIONAL SEARCH REPORT

Intern ...onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 89 06945 A (BIOMEDICAL DESIGN INC) 10 August 1989 (1989-08-10) cited in the application	1-27
A	page 5, line 5 - line 33	1,12,21, 32
A	US 5 420 114 A (CLODMAN PERCY B ET AL) 30 May 1995 (1995-05-30) column 1, line 6 - line 11 column 3, line 3 - line 18	28-31
A	EP 0 121 008 A (NIMNI MARCEL E) 10 October 1984 (1984-10-10) page 3, line 3 - line 18	1,12,21, 32
A	US 4 753 652 A (LANGER ROBERT ET AL) 28 June 1988 (1988-06-28) column 1, line 26 - line 50	1,12,21, 32

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. .onal Application No
PCT/BE 99/00121

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 10262564 A	06-10-1998	NONE	
WO 9219597 A	12-11-1992	IT 1247528 B	17-12-1994
		AU 1448692 A	21-12-1992
US 5843471 A	01-12-1998	AU 1384899 A	31-05-1999
		WO 9924005 A	20-05-1999
		US 6013274 A	11-01-2000
WO 8906945 A	10-08-1989	AT 103789 T	15-04-1994
		AU 3057089 A	25-08-1989
		CA 1307743 A	22-09-1992
		DE 68914384 D	11-05-1994
		DE 68914384 T	28-07-1994
		EP 0364517 A	25-04-1990
		JP 2503064 T	27-09-1990
		JP 2772087 B	02-07-1998
		US 4976733 A	11-12-1990
US 5420114 A	30-05-1995	CA 2126704 A,C	08-01-1995
		US 5498603 A	12-03-1996
EP 0121008 A	10-10-1984	NONE	
US 4753652 A	28-06-1988	NONE	